

Case Report

Monomicrobial necrotizing fasciitis in a white male caused by hypermucoviscous *Klebsiella pneumoniae*

Gudjon L. Gunnarsson,¹ Pernille B. Brandt,² Dorte Gad,¹ Carsten Struve³ and Ulrik S. Justesen²

Correspondence

Gudjon L. Gunnarsson
gudjonleifur@yahoo.com

¹Department of Plastic Surgery, Odense University Hospital, Odense, Denmark

²Department of Clinical Microbiology, Odense University Hospital, Odense, Denmark

³Department of Bacteriology, Mycology and Parasitology, Statens Serum Institut, Copenhagen, Denmark

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We report a case of monomicrobial necrotizing fasciitis caused by hypermucoviscous *Klebsiella pneumoniae* in an immunocompromised white male after travel to China. The *K. pneumoniae* isolate belonged to the K2 serotype, and carried the virulence factors RmpA and aerobactin. To the best of our knowledge this is the first report of necrotizing fasciitis caused by hypermucoviscous *K. pneumoniae* resembling the highly virulent *K. pneumoniae* isolates associated with liver abscess syndrome in Asia.

Introduction

Klebsiella pneumoniae is recognized as an important opportunistic pathogen primarily causing urinary tract infections and bacteraemia. Recently a distinctive syndrome of community-acquired primary liver abscess associated with metastatic infections has emerged, especially in Taiwan and other Asian countries (Fung *et al.*, 2002; Ko *et al.*, 2002; Wang *et al.*, 1998; Yu *et al.*, 2007). These infections occur with high incidence in otherwise healthy individuals and are characteristically caused by highly virulent *K. pneumoniae* isolates belonging to the capsular serotype K1 or K2, expressing a distinct hypermucoviscous phenotype. Two plasmid-encoded virulence factors, RmpA (a regulator of the mucoid phenotype), mediating increased protection against the host immune system by upregulating capsule synthesis, and the iron siderophore aerobactin, enabling the bacteria to obtain iron during infection of the host, are significantly correlated with the high virulence of these invasive strains (Yu *et al.*, 2007, 2008). We report a Danish case of necrotizing fasciitis caused by a hypermucoviscous *K. pneumoniae* isolate of capsule serotype K2, positive for RmpA and aerobactin.

Case report

A 66-year-old white male sought medical attention because of a 2 week history of watery diarrhoea and a 2 day history of a progressive skin infection of his left forefoot. He had just returned from a 2 week holiday in Shanghai, China. The patient neither smoked nor had any history of alcohol abuse. He was slightly overweight and received treatment

for several medical conditions, including a recently diagnosed type 2 diabetes (500 mg metformin once a day), ankylosing spondylitis (25 mg methotrexate weekly, 2 g sulfasalazine and 17.5 mg prednisolone once a day), mild hypertension (5 mg amlodipine once a day) and hypercholesterolaemia (40 mg simvastatin once a day). The patient's podiatry hygiene was optimal and he never suffered from leg ulcers, calluses or corns. He denied any previous wounds of his legs, although he suggested that he might have been bitten by an insect in the ankle without knowing it. The patient's diabetes was mild and recently diagnosed, and his blood sugar level was monitored as stable within the normal range with no hyperglycaemic episodes occurring during his hospital stay.

The patient had consulted his general practitioner a few days earlier because of the diarrhoea and skin infection, and treatment with 800 mg phenoxymethylpenicillin three times a day was initiated, without any effect. On admittance he was tired and showed clinical signs of dehydration but had no fever. He had cellulitis of the entire dorsal forefoot extending circularly halfway up to his knee. During the first hours of observation he suddenly developed signs of sepsis, and in a very short time the foot and lower leg became increasingly painful with the appearance of bullae, and eventually the skin infection evolved to a fulminant necrotizing cellulitis.

Treatment with intravenous 2 g meropenem, 500 mg metronidazole and 600 mg clindamycin three times a day was initiated. Clindamycin was discontinued the following day as Gram-negative bacilli were recovered in blood cultures. Metronidazole was discontinued after 7 days.

When the patient developed bullae, immunoglobulins were given in case this was a sign of the development of a toxic shock syndrome (30 g gamma globulin once a day for 3 days). Intravenous immunoglobulins have been associated with an improved outcome in small studies of streptococcal toxic shock syndrome, which can accompany necrotizing fasciitis caused by group A streptococcus (Darenberg *et al.*, 2003). However, there are no studies to support the use of immunoglobulins to treat necrotizing fasciitis in general.

An operation was performed immediately and the infected skin, subcutis and underlying necrotic fascia were removed. The patient's wounds were treated with a negative pressure device and 12 hours later the leg was re-explored without any signs of further tissue necrosis being found. The patient was clinically stable with signs of infection already subsiding. Five days following the initial operation, skin grafts were applied to the wounds. The patient made a slow recovery due to delayed wound healing complicated by secondary infection with *Pseudomonas aeruginosa*. The patient's diarrhoea subsided without treatment. Antibiotic treatment with meropenem was continued due to signs of right-sided lobar pneumonia considered to be secondary to aspiration. Liver function tests were all normal and there were no further symptoms indicating other organ involvement. After 5 days of meropenem treatment the patient developed severe oral candidiasis that was treated with 100 mg fluconazole once a day. He was discharged after 45 days of hospitalization.

Cultures of blood and wound debris all grew *K. pneumoniae* susceptible to ceftazidime, ceftriaxone, meropenem, ciprofloxacin, gentamicin, tetracycline and polymyxin. All cultures of faeces were negative for *K. pneumoniae*. The *K. pneumoniae* isolates from the wound debris and blood were determined to express the hypermucoviscous phenotype defined as formation of a string (>5 mm) when a loop is passed through a colony (Fang *et al.*, 2004). Capsular serotyping carried out at the International *Escherichia coli* and *Klebsiella* Reference Centre (World Health Organization), Statens Serum Institut, Denmark, revealed that the isolate belonged to the K2 serotype. Furthermore, the isolate carried the virulence factors RmpA and aerobactin as revealed by PCR using specific primers. Thus the isolate exhibited similar characteristics to the highly virulent *K. pneumoniae* isolates associated with liver abscess syndrome in Asia.

Discussion

Historically, *K. pneumoniae* is a rare cause of monomicrobial necrotizing fasciitis, with the earliest case being reported in 1996 (Wong *et al.*, 2004). Intriguingly, the majority of reported cases have been from Asia and the incidence of necrotizing fasciitis caused by *K. pneumoniae* seems to be rising. Thus, *K. pneumoniae* was recently found to be the most commonly identified bacterium in a study of necrotizing fasciitis in Taiwan (Liu *et al.*, 2005). Only

two cases have been reported from Europe and the USA: a newborn child from Turkey with a gangrene of the perineum (Özkan *et al.*, 1997) and a Cambodian male hospitalized with monomicrobial necrotizing fasciitis and septic arthritis after a 6 months stay in the USA (Kohler *et al.*, 2007). It could be speculated that the higher incidence in Asia of necrotizing fasciitis caused by *K. pneumoniae* might be related to the high prevalence of virulent hypermucoviscous *K. pneumoniae* strains in this region. Indeed, necrotizing fasciitis has been reported in relation to the community-acquired *K. pneumoniae* liver abscess syndrome (Dylewski & Dylewski, 1998; Hu *et al.*, 1999; Wong *et al.*, 2004). The vast majority of the highly virulent hypermucoviscous *K. pneumoniae* isolates belong to the K1 or K2 serotype, and the virulence factors RmpA and aerobactin have been shown to correlate with the enhanced virulence of these isolates compared to non-hypermucoviscous K1 and K2 isolates (Yu *et al.*, 2007, 2008). To the best of our knowledge, capsule serotyping of *K. pneumoniae* isolates causing necrotizing fasciitis has only been performed in two cases, and in both of these the infection was caused by isolates of the K1 serotype (Hu *et al.*, 1999; Kohler *et al.*, 2007). However, no previous studies have investigated necrotizing fasciitis isolates for specific virulence factors including the hypermucoviscous phenotype, RmpA and aerobactin. It is likely that our patient was colonized by the *K. pneumoniae* isolate during his recent stay in China, although it cannot be excluded he was already colonized by the *K. pneumoniae* strain in Denmark. Indeed cases of community-acquired liver abscess caused by hypermucoviscous *K. pneumoniae* in patients with no history of travelling to Asia have been reported from Europe and the USA, demonstrating the emergence of these strains outside of Asia (Frazee *et al.*, 2009; Gomez *et al.*, 2007; Karama *et al.*, 2007).

We emphasize the importance of early surgical debridement to reduce bacterial and toxin load in patients with aggressive necrotizing cellulitis, which can evolve to necrotizing fasciitis. Skin signs are usually late in necrotizing fasciitis and it is more common for a patient with necrotizing fasciitis caused by *K. pneumoniae* to have associated organ abscesses signifying that the infection is probably haematogenously spread (Ho *et al.*, 2000; Yu *et al.*, 2007). The fact that our patient had no such foci supports the belief that this case was initially a skin infection, which is less common. The prognosis was subsequently better as the disease is localized to the limb involved and surgical delay is minimized. There are several studies showing higher incidence of opportunistic infections in patients with rheumatological diseases, and a wide array of case reports relate the use of corticosteroids for mild and serious infections. Methotrexate is known to cause alterations in humoral and cellular immunity, but data suggesting it causes immunosuppression when used at low therapeutic doses are debatable (McLean-Tooke *et al.*, 2009). There is, however, no doubt that all individual factors synergistically increase the risk of infection.

To the best of our knowledge this is the first reported case of monomicrobial necrotizing fasciitis caused by *K. pneumoniae* in Western Europe. Furthermore, it is believed to be the first case where it has been established that the infection was caused by a hypermucoviscous *K. pneumoniae* isolate of the K2 serotype carrying the virulence factors RmpA and aerobactin, thereby resembling the highly virulent *K. pneumoniae* isolates associated with liver abscess syndrome in Asia. The rising incidence of severe infections caused by highly virulent *K. pneumoniae* isolates is worrisome and calls for increased international surveillance, including virulence factor assessment, typing and registration of isolates to monitor the geographical spreading of these infections. With this case report we wish to increase the awareness of other serious infections apart from liver abscess caused by hypermucoviscous *K. pneumoniae*, such as necrotizing fasciitis. Due to an ageing population, advances in medical care and treatment modalities, along with more frequent travelling between the continents, infections caused by these aggressive bacteria might become more frequent in our practice in the future.

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